

Review

Efficacy and Safety of Stent, Valves, Vapour ablation, Coils and Sealant Therapies in Advanced Emphysema: A Meta-Analysis

Neeti Rustagi¹ (b, Surjit Singh² (b, Naveen Dutt³ (b, Ashok Kuwal⁴ (b, Kirti Chaudhry⁵ (b, Shashank Shekhar⁶ (b, Richard Kirubakaran⁷

¹Department of Community and Family Medicine, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

²Department of Pharmacology, All India Institute of Medical Sciences Jodhpur, Rajasthan, India

³Department of Pulmonary Medicine, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India ⁴Department of Pulmonary Medicine, Pacific Institute of Medical Sciences, Gyan Nagar, Near Gyan Mandir School, Sector-4,

⁵Department of Dentistry, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

⁶Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India ⁷Department of Biostatistics, Christian Medical College, Vellore, Tamil Nadu, India

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Abstract

Bronchoscopic lung volume reduction (BLVR) methods have emerged as a new treatment option for patients with severe emphysema. Endobronchial valves and coils have been extensively studied. This review assesses efficacy, safety, and cost effectiveness of the BLVR procedures (stent, valves, vapor ablation, endobronchial coils, lung sealant) in patients with severe emphysema. Databases were searched until October 2016, and randomized controlled trials (RCTs) comparing available BLVR procedures to standard medical care or sham bronchoscopy were included. Random effect model and generic inverse variance approach were used for meta-analysis. Out of 381 identified records, 16 RCTs were included. As compared to recommended medical care or sham bronchoscopy, the BLVR procedures are more effective in improving quality of life [SGRQ score (WMD=-6.38; -9.12 to -3.65)] and 6MWT (WMD=24.21; 9.68-38.74) and percentage FEV. (WMD=10.48; 7.07-13.89). Increased risk of serious adverse events (RR=2.18; 1.63-2.93), specifically for chronic pulmonary obstructive disease exacerbations and lower respiratory tract infection combined (RR=1.37; 1.07-1.75), were observed with bronchoscopic interventions, while there was no difference in number of deaths (RR=1.25; 0.79–1.99) and respiratory failure (RR=1.13; 0.57-2.21). The BLVR procedures, especially endobronchial coils, were found to be effective in the management of patients with severe emphysema irrespective of collateral ventilation. However, characterization of patients who would be most benefited from these procedures is required, and effectiveness of these procedures in long run needs to be established.

KEYWORDS: Bronchoscopic lung volume reduction, collateral ventilation, COPD, emphysema Received: 10.05.2018 Accepted: 17.10.2018

INTRODUCTION

Chronic pulmonary obstructive disease (COPD) is a chronic inflammatory disease of the airways and the lungs. It is expected to be the third leading cause of death by 2020 [1]. It is characterized by a spectrum of small airway abnormalities of which emphysema is a major pathological feature. It is associated with alveolar destruction and loss of surrounding elastic tissue and elastic recoil of the lungs that leads to air trapping and increased lung volumes. These altered pathophysiological changes lead to static and dynamic hyperinflation that causes dyspnea, decreased exercise capacity, and impaired quality of life.

Lung volume reduction surgery (LVRS) improves lung function, quality of life, and survival in a specific subset of patients having advanced heterogeneous upper lobe emphysema, but is associated with considerable post-operative complications and mortality (7.9% after 90 days) [2]. Bronchoscopic lung volume reduction (BLVR) procedures appear promising as compared to standard medical care, and safe alternative to LVRS. Endobronchial valves (EBV), one of the most extensively studied bronchoscopic approach, appear to be promising in patients with complete inter-lobar fissure integrity and no collateral ventilation [3]. Other available BLVR modalities of notable interest are endobronchial coils (EBC) [4,5], thermal vapor ablation (TVA) [6,7], emphysematous lung sealant (ELS) [8], and Exhale Airway Stents for Emphysema (EASE) [9]. As evident need exists to assess role of available minimally invasive BLVR procedures, this review was conducted to evaluate their efficacy and safety in management of patients with advanced emphysema.

Eligibility, Literature Search, and Selection Process

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and guidelines of the Cochrane Handbook for Systematic Reviews of Interventions [10].

Studies published in the English language were identified by searching electronic databases and scanning reference list of articles, as well as through correspondence with authors of included studies. We searched PubMed, Google Scholar,

Hiran Magri, Udaipur, Rajasthan, India

Science Citation Index Expanded and Cochrane databases (until July 31, 2018). Randomized controlled trials (RCTs) assessing efficacy and safety of the BLVR procedures compared to recommended medical care were included in this review. Search strategy using the following search terms and their associated medical subject headings was developed: 'emphysema', 'bronchoscopic lung volume reduction', 'endobronchial coil', 'Lung volume reduction coil' and 'airway bypass', 'bronchoscopy glue', 'bronchoscopy sealant', 'bronchoscopy vapor', 'Emphysema airway stent', 'intrabronchial valves' (Table 1).

Two investigators independently screened title and abstract of all search results. Any study found as potentially eligible was read by both authors to determine inclusion. Eligibility criteria were RCTs evaluating BLVR methods compared to recommended medical care or sham bronchoscopy. Both investigators also searched ClinicalTrials.gov and WHO International Clinical Trials Registry Platform search portal without time limits to include any ongoing trials.

Inclusion/exclusion criteria for included trials were: 1) study population: patients with COPD with severe emphysema; 2) any BLVR procedures; 3) study design: an RCT. Studies on animal trial or preclinical studies and non-original articles such as reviews, editorials, letters, and comments were excluded. To resolve disagreements and reaching consensus, multiple rounds of discussion with other co-authors were held.

Data Extraction

Data extraction form was adapted from the Cochrane Airway Review group [11]. It was pilot tested on two included randomly selected studies, and refined accordingly. Two review authors extracted the data that was cross-checked by another review author.

Primary efficacy outcomes for which data were extracted was improvement in patient health status, that is, health-related quality of life measured using the St George's Respiratory Questionnaire (SGRQ) score, which ranges from 0 to 100, with a higher score indicating worse quality of life; exercise capacity measured as 6 Minute Walk Distance (6MWD); and Percentage predicted FEV₁.

Primary safety outcomes assessed were patients experiencing serious adverse events (SAE) reported as deaths, need of hospitalization or any intervention because of occurrence of pneumothorax, COPD exacerbations, lower respiratory infections, hemoptysis, or respiratory failure.

For dichotomous outcome, the number of participants experiencing the event and total in each group was recorded, while for continuous outcomes between-group differences for change in mean and SD at maximum follow-up duration in study trial was included.

Quality Assessment

Methodological quality was independently assessed by two reviewers in accordance with published guidelines [12]. The components assessed were random sequence generation, allocation concealment, blinding of intervention (participants/investigator), blinding of outcome assessment, com-

Table 1. Search shalegy used for this review
Endobronchial coil
OR Lung volume reduction coil
OR Airway bypass
OR Bronchoscopy glue
OR Bronchoscopy sealant
OR Bronchoscopy vapour
OR Airway stent
OR Bronchoscopic lung volume reduction
OR Endobronchial valve
OR Endobronchial valve
OR Intrabronchial valve AND emphysema
OR Emphysema
OR Chronic obstructive pulmonary disease

Table 1 Search strategy used for this review

plete reporting of outcome data, and selective reporting and other bias. Risk of bias for each study was assessed, and in case of any disagreement, the authors resolved it through discussions and building consensus.

Data Synthesis

We used the REVMAN software (Version 5.3. Copenhagen, Denmark) (13) for outcome analysis at the longest follow-up time point. Dichotomous outcomes were pooled as summary relative risk (RR) with 95% confidence intervals (CI), and mean difference with standard error was calculated for continuous outcomes through generic inverse variance (GIV) in which the treatment effect is significant at the 5% level. Heterogeneity between trials was quantified by I² statistic roughly interpreted as follows: <=25%: absent; 26%-39%: unimportant, 40%-60%: moderate; 60%-100%: substantial heterogeneity (12).

Meta-analysis was performed using the random-effects model, as the studies included are not functionally identical. The subjects and intervention performed in studies are different, and thus common effect size cannot be assumed [14].

RESULTS

Out of 381 records identified, 16 RCTs were included [9,15-29], and 1 RCT by Hartman et al. [30] was excluded as it was subgroup analysis of the patients included in a study done by Klooster et al. (Figure 1) [23]. The study conducted by Gompelmann et al. [19] on patients with positive collateral ventilation was a subpart of the TVA study done by Herth et al. [21]. It was included in the final analysis as the study has shown positive results with vapor ablation therapy in patients with positive collateral ventilation, and the weight of the study is only 4.5%. Excluding from the final analysis did not change the overall effect estimate of all the interventions. A total of 1187 patients were studied for the BLVR interventions and compared to either recommended medical care as per international guidelines or Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria or sham bronchoscopy (828 patients) [31]. Out of 16 trials, 7 trials reported on EBV [16,17,20,22,23,26,28]; 3 on EBCs [18,25,27]; 2 on IBV

Table	2. Study Chara	acteristics of inclu	ded trials (n=1	6)		
S. No.	Study	Intervention / Sample size	Control/ Sample size	Disease distribution	Participant characteristic and baseline score on outcomes	Maximum follow-up duration considered
1.	Come et al. [15] – ASPIRE	Emphysematous lung sealant (ELS) plus optimal medical therapy/ 61	Optimal medical therapy alone/ 34	Heterogeneous; Upper lobe predominant emphysema; two subsegments appropriate for treatment in two different upper lobe segments in each lung	Age: treatment 65 years versus control 64 years % female: 41% Participants: treatment n=61 versus control n=34 Disease distribution: heterogeneous Baseline score on outcomes: Median FEV ₁ % predicted (IQR): treatment 29% (23–35) versus control 30% (27 to 38) Median QoL in units total score SGRQ (IQR): treatment 54 units (46–65) versus control 58 units (45–74) Median 6MWD in meters (IQR): treatment 313 m (236–363) versus control 293 m (247–420)	6 months
2.	Criner et al. [16] - LIBERATE	Endobronchial Valve with standard medical management/ 128	Standard medical management/ 62	Heterogeneous emphysema	Age: treatment 64 years versus control 62 years % female: 56% Mean FEV, % predicted (SD): treatment 28.0 %(7.45) versus control 26.2 (6.28) Mean QoL in units total score on SGRQ (SD): treatment 55.15 (14.08) units versus control 53.10 (14.14) units Mean 6MWD in meters (SD): treatment 311 m (81) versus control 302m (79)	12 months Note: patients with little to no collateral ventilation between target and ipsilateral lobes were selected based on assessment with the Chartis Pulmonary Assessment System
3.	Davey et al. [17] - BeLieVeR-HIFi	Unilateral endobronchial valve placement / 25	Sham valve placement / 25	Heterogeneous emphysema	Age: treatment 62 years versus control 63 years % female: 38% Mean FEV ₁ % predicted (SD): treatment 31.6% (10.2) versus control 31.8% (10.5) Mean QoL in units total score on SGRQ (SD): treatment 67.79 units (13.17) versus control 70.65 units (12.48) Mean 6MWD in meters (SD): treatment 342 m (94) versus control 334 m (81)	3 months Note: patients with little to no collateral ventilation were selected based on assessment with the Chartis Pulmonary Assessment System
4.	Deslée et al. [18] - REVOLENS	Nitinol coils plus standard medical management / 50	Standard medical management/ a 50	Both homogeneous ind heterogeneous emphysema	Age: treatment 62 years versus control 63 years % female: 39% Mean FEV ₁ % predicted (SD): treatment 25.7% (7.5) versus control 27.4% (6.2) Mean QoL in units total score on SGRQ (SD): treatment 60.8 units (12.8) versus control 57.1 units (14.1) Mean 6MWD in meters (SD): treatment 300 m (112) versus control 326 m (121)	12 months
5.	Gompelmann et al. [19]	Vapor ablation treatment in addition to standard medical management / 35	Standard medical management consistent with GOLD guidelines/ 19	Heterogeneous emphysema with upper lobe predominance in both lungs with presence of Collateral		12 months Note: post-hoc analysis of STEP-Up trial

et al. [23] - valves/34 medical and STELVIO care/34 heterogeneous Ninane et al. Partial bilateral Sham Heterogeneous [24] placement of control/

Intra-bronchial

valves/37

36

<90%) assessed by multidetector computed tomography scan (MDCT) Herth et al. Unilateral Standard Both Age: treatment 60 years versus 12 months [20] endobronchial medical care homogeneous control 60 years VENT EU based on valve placement and % female: 25% plus usual care GOLD Mean FEV, % predicted (SD): heterogeneous based on GOLD guidelines / treatment 29% (8) versus guidelines / 111 60 control 30% (8) Mean QoL in total score on SGRQ (SD): treatment 59 units (13) versus control 56 units (18) Mean 6MWD in meters (SD): treatment 341 m (108) versus control 360 m (117) Herth et al. Vapor ablation Standard Heterogeneous Age: treatment 64 years versus 6 months [21] treatment in medical emphysema control 63 years STEP-UP addition to with upper lobe % female: 52% management predominance standard medical consistent Mean FEV, % predicted (SD): with GOLD treatment 33.8% (8.2) versus management / 46 in both lungs guidelines / control 33.7% (8.8) 24 Mean QoL in units total score on SGRQ (SD): treatment 57.7 units (15) versus control 57.3 units (20) Mean 6MWD in meters (SD): treatment 356 m (92) versus control 370 m (111.5) **EBV** treatment SoC group/ Age: treatment 65 years versus Kemp et al. Heterogeneous 6 months [22] emphysema control 63 years Note: patients with group/65 32 TRANSFORM % female: 43% little to no collateral Mean FEV, % predicted (SD): ventilation between treatment 29.75% (9.18) versus target and ipsilateral control 32.16 (8.35) lobes were selected Mean QoL in units total score based on assessment on SGRO (SD): treatment 64.34 with the Chartis (14.39) units versus control 58.07 Pulmonary Assessment (13.26) units System Mean 6MWD in meters (SD): treatment 282.46 m (94.41) versus control 320.25 m (91.79) Endobronchial Standard Klooster Homogeneous Age: treatment 58 years versus 6 months valves/34 medical control 59 years heterogeneous % female: 68% Mean FEV₁% predicted (SD): treatment 29% (7) versus control 29% (8) Mean QoL in units total score

Table 2. Study Characteristics of included trials (n=16) (Continue)

Control/

Sample size

Disease

distribution

ventilation (fissure integrity Participant characteristic and

baseline score on outcomes

on SGRQ (SD): treatment 59.1 units (13.7) versus control 59.3

Mean 6MWD in meters (SD): treatment 372 m (90) versus control 377 m (84)

Age: treatment 61 years versus

Mean FEV₁% predicted (SD):

6 months

units (11.6)

control 62 years

% female: 41%

Maximum follow-up

duration considered

Intervention /

Sample size

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S. No. Study

6.

7.

8.

9.

10.

46

S. No.	Study	Intervention /	Control/	Disease	Participant characteristic and	Maximum follow-up
	,	Sample size	Sample size	distribution	baseline score on outcomes	duration considered
					treatment 35% (10) versus control 32% (7) Mean QoL in units total score on SGRQ (SD): treatment 61 units (11) versus control 60 units (13) Mean 6MWD in meters (SD): treatment 337 m (106) versus control 346 m (123)	
11.	Sciurba et al. [26] -VENT US	Unilateral endobronchial valve placement plus usual care based on GOLD guidelines / 220	Standard medical care based on GOLD guidelines / 101	Both homogeneous and heterogeneous emphysema	Age: treatment 65 years versus control 65 years % female: 57% Mean FEV ₁ % predicted (SD): treatment 30% (8) versus control 30% (8) Mean QoL: not reported Mean 6MWD in meters (SD): treatment 334 m (87) versus control 351 m (83)	12 months
12.	Sciurba et al. [25] -RENEW	Nitinol coils plus usual care based on GOLD guidelines / 158	Usual care based on GOLD guidelines / 157	Both heterogeneous and homogeneous emphysema	Age: treatment 63 years versus control 64 years % female: 52.4% Mean FEV ₁ % predicted (SD): treatment 25.7% (6.3) versus control 26.3% (6.7) Mean QoL in units total score on SGRQ (SD): treatment 60.1 units (12.8) versus control 57.4 units (14.8) Mean 6MWD in meters (SD): treatment 312.0 m (79.1) versus control 302.7 m (79.3)	12 months
13.	Shah et al. [9] - EASE	Exhale drug eluting stent / 208	Sham bronchoscopy/ 107	Homogeneous emphysema	Age: treatment 64 years versus control 64 years % female: 49% Mean FEV ₁ % predicted (SD): treatment 23.2% (6.1) versus control 23.6% (7.2) Mean QoL in units total score on SGRQ (SD): treatment 56.6 units (12.9) versus control 58.04 units (13.25) Mean 6MWD in meters (SD): treatment 302 m (88) versus control 297 m (85)	12 months
14.	Shah et al. [27] – RESET	LVRC (RePneu coil) / 23	Best medical care / 24	Both homogeneous and heterogeneous emphysema	Age: treatment 62 years versus control 65 % female: 38% Mean FEV ₁ % predicted (SD): treatment 27.2% (8.0) versus control 28.9% (6.9) Mean QoL in units total score on SGRQ (SD): treatment 65.2 units (8.7) versus control 53.1 units (13.8) Mean 6MWD in meters (SD): treatment 293.7 m (75.5) versus control 346.2 m (110.9)	90 days after final treatment
15.	Valipour et al. [28] – IMPACT	Endobronchial valves / 43	Optimal medical care / 50	Homogeneous	Age: treatment 64 years versus control 63 years % female: 61% Mean FEV ₁ % predicted (SD): treatment 28.4% (6.3) versus	3 months

Table 2. Study Characteristics of included trials (n=16) (Continue)
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S. No.	Study	Intervention / Sample size	Control/ Sample size	Disease distribution	Participant characteristic and baseline score on outcomes	Maximum follow-up duration considered
					control 29.9% (6.6) Mean QoL in units total score on SGRQ (SD): treatment 63.2 units (13.7) versus control 59.3 units (15.6) Mean 6MWD in meters (SD): treatment 308 m (91) versus control 328 m (93)	
16.	Wood et al. [29]	Partial bilateral placement of Intra-bronchial valves / 142	Sham control/ 135	Heterogeneous	Age: treatment 65 years versus control 65 years % female: 43% Mean FEV ₁ % predicted (SD): treatment 29.8% (7.5) versus control 29.7% (7.9) Mean QoL in units total score on SGRQ (SD): treatment 54.8 units (15.5) versus control 57.1 units (15.2) Mean 6MWD in meters (SD): treatment 314.1 m (88.6) versus control 308.6 m (81.6)	6 months

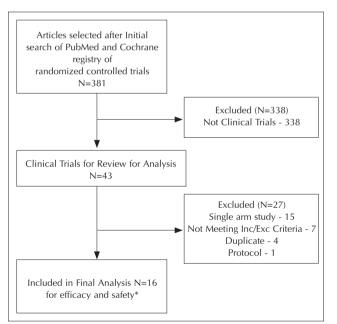


Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis flow diagram

*-Gompelmann et al. [19] is a post-hoc analysis of step-up triala

[24,29]; 2 on TVA [4,19]; 1 on ELS [15] and 1 on airway stents (Table 2) [9].

Characteristics of Patients Included

Eight trials included patient predominantly with heterogeneous emphysema [15-17,19,21,22,24,29]; two trials were on patients with homogeneous emphysema [9,28]; and rest trials had patients with both heterogeneous and homogeneous emphysema [18,20,23,25-27]. Mean age of participants was about 60 years. Inclusion of white ethnicity participants (90% or above) was reported in seven trials [9,16,20,21,23,25,26].

A sample size of more than 100 in either or both groups was included in five trials [9,16,25,26,29]. The trials included in the meta-analysis followed patients for duration of 3-12 months.

Risk of Bias

A tool from the Cochrane Collaboration was used to assess the risk of bias of each study. Low risk of performance and detection bias by comparing BLVR to sham bronchoscopy was observed for EBV [17,22], airway stent [9], and IBV trial [24,29]. Risk of bias related to randomization, allocation concealment, attrition, and selective reporting was found to be low for the majority of trials (Figure 2).

Efficacy of Interventions

For studying efficacy outcome, lung sealant trial (15) was excluded from efficacy meta-analysis as it was prematurely terminated and possessed a high risk of bias (Figure 2). Quality of evidence for the efficacy of intervention was assessed for patients with no collateral ventilation undergoing the bronchoscopic procedure for EBV (Table 3) and for EBC (Table 4). Quality of evidence was not assessed for rest of the BLVR modalities as only one or two trials were available with small sample size.

Patient-Centric Outcomes

SGRQ

Pooled analysis revealed that the BLVR procedures significantly reduced the mean SGRQ score compared to control group [WMD=-6.38 (95% Cl; -9.12 to -3.65); l²=76%]. In subgroup analysis, significant reduction in the SGRQ score was observed for EBC trials [WMD=-9.21; 95% Cl; -11.41 to -7.02); l²=0, high quality of evidence] and for EBV in patients with no collateral ventilation [WMD=-7.00; 95% Cl; -9.85 to -4.14); l²=52%, high quality of evidence].

Significant reduction in the SGRQ score was also seen with vapor ablation [WMD=-9.70 (95% CI; -15.7 to -3.70)].

Table 3. GRADE and Summary of findings table for lung volume reduction bronchial valves as compared to standard care in severe emphysema

			Certainty	assessment			No. of pat	tients	Effe	ct		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lung volume reduction interventions		Relative (95% Cl)	Absolute (95% CI)	Certainty	Importance
Assessii ventilat	· ,	Bronchos	scopic Lung vol	ume Reductio	on on St. Geo	rge Respiratory (Questionnaire (S	SGRQ) sco	re – Endobi	onchial valve	s with no c	ollateral
7	randomized trials		serious ^b	not serious	not serious	strong association	570	344	-	MD 7.00 lower (9.85 lower to 4.14 l ower)	φφφφ HIGH	CRITICAL
6 Minu	te Walk Test -	Endobro	nchial valves wi	ith no collater	al ventilation							
7	randomized trials			not serious	not serious ^d	strong association	573	346	-	MD 39.86 higher (18.42 higher to 61.29 higher)	↔ ↔ O MODERA	IMPORTANT TE
%FEV1	- Endobroncl	hial valve	s with no collate	eral ventilatio	n							
7	randomized trials	not serious	not serious	not serious	not serious	none	557	322	-	MD 18.82 higher (14.18 higher to 23.47 higher)	⇔ ⊕⊕ HIGH	CRITICAL
Total S€	erious Adverse	e Events (S	SAE) - Endobron	nchial valves								
6	randomized trials	serious	not seriouse	not serious	not serious	strong association	211/515 (41.0%)	56/304 (18.4%)	RR 3.13 (1.48– 6.60)	392 more per 1,000 (from 88 more to 1000 more)	⇔⇔⇔ HIGH	CRITICAL
Death -	Endobronchi	ial valves										
7	randomized trials	serious		not serious	serious ^f	none	21/626 (3.4%)	9/364 (2.5%)	RR 1.14 (0.55– 2.39)	3 more per 1,000 (from 11 fewer to 34 more)	⊕⊕⊕O MODERA	
			onchial valves									
7	randomized trials		not serious	not serious	serious ^f	none	156/626 (24.9%)	92/364 (25.3%)	RR 0.99 (0.82– 1.19)	3 fewer per 1,000 (from 45 fewer to 48 more)	↔ ↔ O MODERA	
Respira	tory Failure R	equiring I	Mechanical Ven	ntilation - Ende	obronchial va	lves						
6	randomized trials	not serious	not serious	not serious	serious ^f	none	11/561 (2.0%)	5/332 (1.5%)	RR 1.06 (0.38– 2.95)	1 more per 1,000 (from 9 fewer to 29 more)	⊕⊕⊕O MODERA	

Patients with upper lobe emphysema with positive collateral ventilation also scored well with TVA [WMD=-8.40 (95% Cl; -17.51-0.71)] (Figure 3a).

6MWT

The BLVR procedures as per pooled analysis improved 6MWT significantly as compared to control group

[WMD=24.21; (95% CI; 9.68-38.74); I²=83%]. Subgroup analysis showed significant improvement in 6MWT for EBCs [WMD=33.52; (95% CI; 5.88-61.16); I²=65%, very low quality of evidence] and among patients with no collateral ventilation undergoing EBV [WMD=39.86; (95% CI; 18.42-61.29); I²=77%, moderate quality of evidence]. For subgroup undergoing IBV procedure, the patients in control group **Table 4.** GRADE and Summary of findings table for lung volume reduction endobronchial coils as compared to standard care in severe emphysema

			Certainty	assessment			No. of pa	tients	Effe	ect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lung volume reduction interventions	Standard care		Absolute (95% Cl)	Certainty	Importance
Assessi	ng Efficacy of	Bronchos	scopic Lung vol	ume Reductio	on on St. Geo	rge Respiratory (Questionnaire (S	SGRQ) sco	re - Bronch	ial coils		
3 6 Minu	randomized trials te Walk Test -		serious	not serious	not serious	strong association	231	230	230	MD 9.21 lower (11.41 lower to 7.02 lower)	⇔⇔⇔ HIGH	CRITICAL
3	randomized			pot	serious℃	popo	211	213		MD 33.52		IMPORTAN'
	trials		senous	not serious	senous-	none	211	213	-	higher (5.88 higher to 61.16 higher)	VERY	IMPORIAN
%FEV ₁	- Bronchial C											
3	randomized trials	not serious	serious ^b	not serious	serious ^c	none	210	213	-	MD 7.1 higher (0.58 lower to 14.78 higher		CRITICAL
Total Se	erious Adverse	e Events (S	SAE) - Bronchial	Coils								
3	randomized trials	not serious	not serious	not serious	not serious	none	89/231 (38.5%)	53/230 (23.0%)	RR 1.63 (1.23– 2.16)	145 more per 1,000 (from 53 more to 267 more)	♦	CRITICAL
Death -	Bronchial Co	oils										
3	randomized trials	not serious	not serious	not serious	serious ^d	none	14/231 (6.1%)	11/230 (4.8%)	RR 1.27 (0.59– 2.73)	13 more per 1,000 (from 20 fewer to 83 more)	⊕⊕⊕O MODERA	Critical Te
COPD	Exacerbation	- Bronch	ial Coils									
3	randomized trials	not serious	not serious	not serious	not serious	strong association	76/231 (32.9%)	36/230 (15.7%)	RR 2.06 (1.46– 2.92)	166 more per 1,000 (from 72 more to 301 more)	⇔⇔⇔ HIGH	CRITICAL
Respira	tory Failure R	equiring l	Mechanical Ver	ntilation - Bror	nchial Coils							
3	randomized trials	not serious	not serious	not serious	serious ^d	none	7/231 (3.0%)	9/230 (3.9%)	RR 0.80 (0.30– 2.16)	8 fewer per 1,000 (from 27 fewer to 45 more)	↔ ↔ ↔ MODERA	CRITICAL TE

significantly improved over intervention group [WMD=-19.54; (95% CI; -37.11 to -1.98); I²=0] (Figure 3b).

Outcomes Related to Lung Function

Percent change in % predicted FEV₁

Pooled analysis for mean change in % predicted FEV_1 significantly improved for patients undergoing bronchoscopic procedure [WMD=10.48; (95% CI; 7.07-13.89); I²=91%]. Subgroup analysis for patients with no collateral ventilation

undergoing EBV procedure (WMD=18.82; 95% CI; 14.18-23.47); I²=35%, high quality of evidence]; EBC trials [(WMD=7.10; 95% CI; -0.58-14.78); I²=87%, low quality of evidence] and TVA (WMD=14.70; 95% CI; 7.80-21.60) showed promising results over standard medical care or sham bronchoscopy. The patients with positive collateral ventilation also were significantly benefited by TVA intervention as compared to control group (WMD=14.60; 95% CI; 3.00-26.20) (Figure 3c).

Safety of bronchoscopic intervention

All 15 studies were included for meta-analysis as reporting of adverse events is unlikely to get affected due to high risk of bias.

Serious Adverse Events

Serious adverse events were defined as incidence of deaths or events that required or prolonged hospitalization or were life-threatening. Pooled analysis [(RR=2.18; 95% Cl; 1.63-2.93); l²=62%] and subgroup analysis for EBC [(RR=1.63; 95% Cl; 1.23-2.16); l²=0, high quality of evidence], EBV [(RR=3.13; 95% Cl; 1.48-6.60); l²=83%, high quality of evidence], IBV [(RR=2.71; 95% Cl; 1.24-5.93); l²=13%], and ELS [(RR=3.34; 95% Cl; 1.57-7.12) reported significantly higher SAE for intervention group as compared to control group (Figure 4a).

Death and Respiratory Failure

No significant difference was observed in the risk of mortality (Figure 4b) and respiratory failure requiring mechanical ventilation (Figure 4c) in both pooled and subgroup analysis

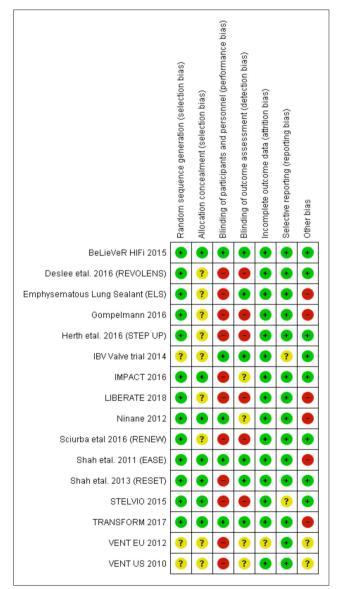


Figure 2. Risk of bias summary for bronchoscopic lung volume reduction interventions studies in patients with severe emphysema

(p>0.05). Heterogeneity was found to be absent ($I^{2=0}$), and the quality of evidence was moderate for both EBC (Table 4) and EBV (Table 3).

Combined Episodes of COPD Exacerbations and Lower Respiratory Infections (LRTI)

Significantly higher episodes of COPD exacerbations and LRTI combined [RR=1.37; 95% CI; 1.07-1.75); I²=49%] (Figure 4d) were observed for patients with BLVR in pooled analysis. Subgroup analysis revealed higher risk of COPD exacerbations and LRTI episodes for patients undergoing bronchoscopic procedures in case of EBC [RR=2.06; 95% CI; 1.46-2.92); I²=0, high quality of evidence] (Table 4) and TVA [RR=3.38; 95% CI; 1.11-10.27) but not for EBV [RR=0.99; 95% CI; 0.82-1.19); I²=0, moderate quality of evidence] (Table 3) and airway stents [RR=1.89; 95% CI; 0.94-3.80), as compared to control group.

Publication bias

Publication bias was low as the funnel plot for 16 studies appears to be symmetrical around the intervention effect estimate. This review includes only randomized trials, and does not take into account the pilot studies and cohort studies previously published for one or more bronchoscopic interventions. As all types of studies were published for bronchoscopic intervention, publication bias is not detected.

Clinical and Research Consequences

Despite the maximal pharmacological treatment and rehabilitation, the patients with COPD with moderate to severe emphysema remain symptomatic. LVRS has shown long-term benefit only in a specific subset of patients with considerable post-operative morbidity and mortality, and thus the BLVR procedures have evolved in the quest of a safer treatment option for patients with advanced emphysema.

Our systematic review highlights the safety and efficacy of the BLVR procedures over a period of 3-12 months in managing patients with advanced severe emphysema. The inclusion of randomized trials for comparing the BLVR procedures to medical care or sham bronchoscopy provides robust estimates regarding benefits of existing methods as compared to published meta-analyses [32,33]. The strengths of our metaanalysis are that the GIV approach was used. The change from baseline scores was compared for both groups for patient-centric and lung function outcomes using random effect model to account for between studies variance and to ensure generalizability of results.

Earlier trials [20,26] for EBV suggested higher efficacy in patients with no collateral ventilation for both heterogeneous and homogeneous emphysema. In this review, to determine the efficacy of EBV, post-hoc analysis data of patients with no collateral ventilation in Herth et al. [20] and Sciurba FC [26] trials were included along with other trials [16,17,20,22,23,28] that studied only patients with no collateral ventilation.

In the intervention group, significant improvement was observed, and minimal clinically important difference (MCID) was achieved for the quality of life, 6MWD, and percentage change in predicted FEV₁. Higher risk of serious respiratory adverse events especially pneumothorax and

COPD and LRTI exacerbations is also significantly high in the intervention group, and it underscores the need for careful and planned follow-up in patients recruited for EBV. Pooled mean differences for EBCs showed statistically significant improvement in all studied parameters and more than respective MCIDs for SGRQ score and 6MWT. Suitability of EBCs in patients who are ineligible for either

1.1.2 Bronchial coils Deslee etal. 2016 (REVOLENS) Sciurba etal 2016 (RENEW) Shah etal. 2013 (RESET) Subtotal (95% CI)	-8.9	SE 2.449	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Deslee etal. 2016 (REVOLENS) Sciurba etal 2016 (RENEW) Shah etal. 2013 (RESET) Subtotal (95% CI)	-8.9	2.449					
Sciurba etal 2016 (RENEW) Shah etal. 2013 (RESET) Subtotal (95% CI)	-8.9	2.449					
Shah etal. 2013 (RESET) Subtotal (95% CI)			50	50		-10.60 [-15.40, -5.80]	-
Subtotal (95% CI)	0.00		158	157	9.1%	-8.90 [-11.50, -6.30]	•
	-0.30	4.0205	23 231	23 230	5.4% 22.1%	-8.36 [-16.24, -0.48] -9.21 [-11.41, -7.02]	•
Heterogeneity: Tau ² = 0.00; Chi ² =		1); l² = 0%					
Test for overall effect: Z = 8.22 (P <	< 0.00001)						
1.1.3 Endobronchial valves with	no collateral ventil	ation					
BeLieVeR HIFi 2015	-5.06	4.8262	23	24	4.5%	-5.06 [-14.52, 4.40]	
IMPACT 2016	-9.64	2.2786	37	48	7.8%	-9.64 [-14.11, -5.17]	-
LIBERATE 2018	-7.05	2.409	128	62	7.7%	-7.05 [-11.77, -2.33]	-
STELVIO 2015	-14.71	3.3595	34	34	6.3%	-14.71 [-21.29, -8.13]	
TRANSFORM 2017	-6.5	2.6245	65	32	7.3%	-6.50 [-11.64, -1.36]	-
VENT EU 2012	-4	3.3885	44	19	6.3%	-4.00 [-10.64, 2.64]	-+
VENT US 2010	-3.4	1.5471	220	101	8.8%	-3.40 [-6.43, -0.37]	
Subtotal (95% CI)			551	320	48.7%	-7.00 [-9.85, -4.14]	♦
Heterogeneity: Tau ² = 7.26; Chi ² = Test for overall effect: Z = 4.80 (P <		05); I² = 52%)				
1.1.4 Bronchial vapor ablation							
Herth etal. 2016 (STEP UP) Subtotal (95% CI)	-9.7	3.0613	42 42	23 23		-9.70 [-15.70, -3.70] -9.70 [-15.70, -3.70]	•
Heterogeneity: Not applicable Test for overall effect: Z = 3.17 (P =	= 0.002)						
1.1.5 Bronchial stent							
Shah etal. 2011 (EASE) Subtotal (95% CI)	-2	7.5595	208 208	107 107		-2.00 [-16.82, 12.82] -2.00 [-16.82, 12.82]	•
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.26 (P =	= 0.79)						
1.1.6 Intrabronchial valves							
IBV Valve trial 2014	3.56	1.6805	142	135	8.7%	3.56 [0.27, 6.85]	⊢
Ninane 2012	-0.7	3.2052	37	36	6.5%	-0.70 [-6.98, 5.58]	÷.
Subtotal (95% CI)			179	171	15.2%	2.30 [-1.50, 6.11]	•
Heterogeneity: Tau ² = 2.53; Chi ² = Test for overall effect: Z = 1.19 (P =		4); l² = 28%					
1.1.7 Vapor ablation in collateral	ventilation positive	9					
Gompelmann 2016	-8.4	4.65	35	19	4.7%	-8.40 [-17.51, 0.71]	_ _
Subtotal (95% CI)	-0.4	т. U J	35	19	4.7%	-8.40 [-17.51, 0.71] -8.40 [-17.51, 0.71]	•
Heterogeneity: Not applicable Test for overall effect: Z = 1.81 (P =	= 0.07)						
Total (95% CI)			1246	870	100.0%	-6.38 [-9.12, -3.65]	
Heterogeneity: Tau ² = 19.64; Chi ² = Test for overall effect: Z = 4.57 (P <		0.00001); l ²	= 76%				-100 -50 0 50 10 Favours [BLVR] Favours [control]

Figure 3a. Efficacy outcomes of bronchoscopic lung volume reduction interventions in patients with severe emphysema: SGRQ Score

LVRS or EBVs and evidence of both efficacy and safety up to 12 months of follow-up is noteworthy. High risk of LRTI (pneumonia) reported in EBC is attributed to local inflammation, ischemia, and scarring of lung parenchyma and not due to infections [25]. Similarly, observed the high risk of pneumothorax is associated with atelectasis, and it rarely requires surgical intervention for management [34]. Currently, the related evidence regarding the efficacy of

Study or Subgroup	Mean Difference	SE	xperimental Total		Weight	Mean Difference IV, Random, 95% C	Mean Difference I IV, Random, 95% CI
1.2.1 Bronchial Coils						,,,	
Deslee etal. 2016 (REVOLENS)	21	16.4289	50	50	5.9%	21.00 [-11.20, 53.20]	
Sciurba etal 2016 (RENEW)		11.3378	138	140	6.9%	19.00 [-3.22, 41.22]	
Shah etal. 2013 (RESET)		15.8166	23	23	6.0%		
Subtotal (95% CI)	00.0	10.0100	211	213	18.9%		
Heterogeneity: Tau² = 387.30; Chi² Test for overall effect: Z = 2.38 (P		0.06); l² = 6	65%				
1.2.2 Endobronchial valves with	no collateral venti	lation					
BeLieVeR HIFi 2015	33	18.547	23	24	5.5%	33.00 [-3.35, 69.35]	+
IMPACT 2016	39.9	12.9091	40	50	6.6%	39.90 [14.60, 65.20]	
LIBERATE 2018		12.6126	128	62	6.7%	39.31 [14.59, 64.03]	
STELVIO 2015		13.425	34	34		74.00 [47.69, 100.31]	
TRANSFORM 2017		15.373	65	32		78.70 [48.57, 108.83]	
VENT EU 2012		11.3902	44	19	6.9%		
						3.00 [-19.32, 25.32]	
VENT US 2010 Subtotal (95% CI)	14.0	13.7247	220 554	101 322		14.60 [-12.30, 41.50] 39.86 [18.42, 61.29]	
Heterogeneity: Tau ² = 641.34; Chi ²		= 0.0002); I					· · · · ·
Test for overall effect: Z = 3.64 (P	= 0.0003)						
1.2.3 EBV with collateral ventilat							
VENT EU 2012 Subtotal (95% CI)	2	4.1135	67 67	40 40	8.1% 8.1%	2.00 [-6.06, 10.06] 2.00 [-6.06, 10.06]	•
Heterogeneity: Not applicable Test for overall effect: Z = 0.49 (P	= 0.63)						
1.2.4 Bronchial Vapor Ablation							
Herth etal. 2016 (STEP UP) Subtotal (95% CI)	30.5	16.3268	42 42	23 23	5.9% 5.9%	30.50 [-1.50, 62.50] 30.50 [-1.50, 62.50]	
Heterogeneity: Not applicable Test for overall effect: Z = 1.87 (P =	= 0.06)						
1.2.5 Bronchial Stent							
Shah etal. 2011 (EASE) Subtotal (95% CI)	-16	11.8195	208 208	107 107	6.8% 6.8%	-16.00 [-39.17, 7.17] -16.00 [-39.17, 7.17]	
Heterogeneity: Not applicable Test for overall effect: Z = 1.35 (P =	= 0.18)						
1.2.6 Intrabronchial valves							
IBV Valve trial 2014		9.2067	120	133	7.4%	-20.62 [-38.66, -2.58]	
Ninane 2012 Subtotal (95% CI)	0	39.2427	37 157	36 169	2.5%	0.00 [-76.91, 76.91] -19.54 [-37.11, -1.98]	
Heterogeneity: Tau ² = 0.00; Chi ² =		61); I² = 0%		105	5.070	-13.54 [-37.11, -1.30]	•
Test for overall effect: Z = 2.18 (P	= 0.03)						
1.2.7 STEP UP in collateral venti	•	47.05	05	10	F 00/	40.001.00 70.45.001	
Gompelmann 2016 Subtotal (95% CI)	10.8	17.65	35 35	19 19		10.80 [-23.79, 45.39] 10.80 [-23.79, 45.39]	
Heterogeneity: Not applicable Test for overall effect: Z = 0.61 (P :	= 0.54)						
Total (95% CI)			1274	893	100.0%	24.21 [9.68, 38.74]	▲
Heterogeneity: Tau² = 662.84; Chi² Test for overall effect: Z = 3.27 (P		< 0.00001); l² = 83%				-100 -50 0 50 100

Figure 3b. Efficacy outcomes of bronchoscopic lung volume reduction interventions in patients with severe emphysema: 6MWT

EBCs is not strong as the two out of three included trials with large sample size has a high risk of performance bias (participants not blinded to intervention) and detection bias [18,25]. Higher risk of serious respiratory adverse events in EBC group emphasizes the need for planned follow-up in patients opting for EBC.

14.1 Brochail Colis Deside etal. 2016 (RE-VEW) 11 2.5611 50 8.4% 11.00 (6.00, 16.00) Stand etal. 2016 (RE-VEW) 1.5 0.8271 137 140 9.9% 1.50 [C1.10, 2.012] Stand etal. 2016 (RE-VEW) 1.02 4.47 23 23 5.7% 10.62 (1.12, 2.012] Stand etal. 2016 (RE-VEW) 1.02 4.42 23 23 5.7% 10.62 (1.12, 2.012] Heterogenetly Tax ² = 37.61; Ch ² = 15.22, df = 2 (P = 0.0006); P = 87% Test (Fromoschial valves with no collateral ventilation 24 24.05% 7.10 (4.58, 14.73.06) MEACT 2016 10.5 4.97 4.67 1.50 (15.3, 18.57) 1.00 (1.33, 18.57) MERATE 2018 17.86 4.17 4.54 1.60 (1.77, 27.83) TENUSORU 2015 17.8 4.127 220 101 6.5% 2.00 (6.06, 10.06) 1.01 (1.10, 17.7, 27.83) TENUSORU 2017 2.3 4.31 5.57 3.22 37.85 18.82 (1.41.8, 23.47) VENT EU 2012 17.9 4.127 2.20 16.05, 10.06] 1.028 1.028 1.028 1.028 1.028 1.028 1.028 1.028 1.028	Study or Subgroup	Mean Difference	E SE	Experimental Total		Weight	Mean Difference IV, Random, 95% C	Mean Differe	
Deales etal. 2016 (REVOLENS) 11 2.5511 50 50 8.4% 11.00 (8.00, 66.00) Stands etal. 2016 (REVEN) 1.50 2.8071 137 140 9.9% 5.75 10.62 (1.12, 2.0.12) Subtratel. 2015 (REVEN) 1.50 2.40 2.10 2.13 2.40% 7.10 (0.56, 14.76) Heinoprenity Tar 37.61: Chit = 15.22, di = 2 (P = 0.0005); P = 87% 2.13 2.40% 7.10 (0.56, 14.76) Selvice III 12015 2.09 8.2472 2.3 2.4 3.1% 2.090 (1.47, 3.76) JERANE T2015 2.09 8.2472 2.3 2.4 3.1% 2.090 (1.47, 3.76) JERANE T2016 1.76 5.113 3.4 3.4 5.6% 17.80 (7.77, 27.83) JERANE F2018 1.76 5.677.4 4.19 9.4.18, 23.477 2.30 (1.20, 13.9, 3.00) VENT EVU2012 1.76.77 4.10 1.95.5% 1.70 (1.31, 3.00) 4.16 (1.00, 1.00) Subtrate (6% C) 1.79.4127 2.00 (1.60, 1.00, 1.00) 4.16 (1.00, 1.00, 1.00) 4.16 (1.00, 1.00, 1.00) 4.16 (1.00, 1.00, 1.00) Subtrate (6% C) 4.17.3 (5.20, 5 4.1 2.3 <t< td=""><td></td><td>mean philerende</td><td>01</td><td>Total</td><td>Total</td><td>Weight</td><td>11, 14, 14, 14, 14, 14, 14, 14, 14, 14,</td><td></td><td></td></t<>		mean philerende	01	Total	Total	Weight	11, 14, 14, 14, 14, 14, 14, 14, 14, 14,		
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Subola (95% C) 210 213 24.0% 7.10 [0.5,8, 14.78] Heterogeneity: Tax' = 37.61; Chi ² = 15.22; df = 2 (P = 0.0005); P = 67% Electro veeral field: 2 = 13.10 (P = 0.0005); P = 67% BelieVer Hill 2015 20.9 8.2472 23 24 3.1% 20.90 [4.74, 37.06] MPACT 2016 10.5 46.77 43 50 5.9% 10.50 [1.3, 19.67] BERATE 2018 17.99 4.2412 28 6.2 6.4% 17.80 [5.06, 26.23] STELVO 2015 17.8 5.1153 34 34 5.4 6.4% 17.80 [5.06, 26.23] STELVO 2015 17.8 5.1153 34 34 5.4 6.4% 17.80 [5.06, 20.23] STELVO 2015 17.8 5.1153 34 34 5.4 6.5% 17.90 [9.80, 26.00] STELVO 2015 17.8 5.1153 20.0 14.9 2.4 2.2 5.2% 10.20 20.81 37.79] Heterogeneity: Tax' = 13.59; Chi ² = 9.29; df = 6 [P = 0.16]; P = 35% Test for overall effect: 2 = 7.36 (P = 0.20001) 14.3 Endobronchial valves with collateral ventilation Heterogeneity: Not applicable Test for overall effect: 2 = 7.36 (P = 0.0001) 14.4 Bronchial Vaper Ablation Heterogeneity: Not applicable Test for overall effect: 2 = 1.48 (P < 0.0001) 14.5 Bronchial Stert Bive additione (FSK Ch) Heterogeneity: Not applicable Test for overall effect: 2 = 1.48 (P < 0.0001) 14.5 Bronchial Stert Bive additione (FSK Ch) Heterogeneity: Not applicable Test for overall effect: 2 = 1.48 (P < 0.0001) 14.5 Bronchial Stert Bive additione (FSK Ch) 14.6 Stronchial Stert Bive additione (FSK Ch) 14.7 STEP UP) 14.7 STEP UP) 14.7 STEP UP) 14.7 Step Chi 2 20 0 0 0 0 Not estimable Subtotal (FSK Ch) 14.8 Endobronchial stert Bive additione (FSK Ch) 14.8 Endobronchial Stert Bive additione (FSK Ch) 14.9 Stop Chi 12.01% 24.15 [3.54, -0.76] 15.15 [3.54, -0.76] 16.15 (3.54, -0.76] 17.10 [5.55 (3.54, -0.76] 18.12 10.0% 25.15 [3.54, -0.76] 19.4.7% 14.60 [3.00, 26.20] 14.7 STEP UP in collateral ventilation positive Sometrian 2016 14.7 STEP UP in collateral ventilation positive Sometrian 2016 15.2 3.3 (P = 4.7% 14.60 [3.00, 26.20] 14.7 STEP UP in collateral ventilation positive Sometrian 2016 14.8 5.92 35 19 4.7% 14.60 [3.00, 26.20] 14.7 STEP UP in collateral ventilation positive Sometrian 2016 14.8	. ,								_
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Subtotal (95% Cl) 208 107 10.1% 0.95 [-0.16, 2.06] Heterogeneity: Not applicable Test for overall effect: Z = 1.68 (P = 0.09) 1.4.6 Intrabronchial valves IBV Valve trial 2014 -2.15 0.7107 118 132 10.0% -2.15 [-3.54, -0.76] Ninane 2012 0 0 0 Not estimable Subtotal (95% Cl) 118 132 10.0% -2.15 [-3.54, -0.76] Heterogeneity: Not applicable 118 132 10.0% -2.15 [-3.54, -0.76] 118 Test for overall effect: Z = 3.03 (P = 0.002) 118 132 10.0% -2.15 [-3.54, -0.76] 14.60 [3.00, 26.20] ALAT STEP UP in collateral ventilation positive 118 132 10.0% -2.15 [-3.54, -0.76] 14.60 [3.00, 26.20] Subtotal (95% Cl) 14.6 5.92 35 19 4.7% 14.60 [3.00, 26.20] 14.60 Heterogeneity: Not applicable 14.6 5.92 35 19 4.7% 14.60 [3.00, 26.20] 14.60 Test for overall effect: Z = 2.47 (P = 0.01) 1236 856 100.0% 10.48 [7.07, 13.89] 14.60 10.48 [7.07, 13.89] </td <td>1.4.5 Bronchial Stent</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	1.4.5 Bronchial Stent								
Heterogeneity: Not applicable Test for overall effect: $Z = 1.68 (P = 0.09)$ 1.4.6 Intrabronchial valves IBV Valve trial 2014 -2.15 0.7107 118 132 10.0% -2.15 [-3.54, -0.76] Ninane 2012 0 0 0 Not estimable Subtotal (95% CI) 118 132 10.0% -2.15 [-3.54, -0.76] Heterogeneity: Not applicable 118 132 10.0% -2.15 [-3.54, -0.76] Test for overall effect: $Z = 3.03 (P = 0.002)$ 118 132 10.0% -2.15 [-3.54, -0.76] 1.4.7 STEP UP in collateral ventilation positive 118 132 10.0% -2.15 [-3.54, -0.76] Gompelmann 2016 14.6 5.92 35 19 4.7% 14.60 [3.00, 26.20] Subtotal (95% CI) 35 19 4.7% 14.60 [3.00, 26.20] Image: Coll of the coll of	Shah etal. 2011 (EASE)	0.95	0.5654	208	107	10.1%	0.95 [-0.16, 2.06]	•	
Test for overall effect: $Z = 1.68 (P = 0.09)$ 1.4.6 Intrabronchial valves BV Valve trial 2014 -2.15 0.7107 118 132 10.0% -2.15 [-3.54, -0.76] Ninane 2012 0 0 0 Not estimable Subtotal (95% CI) 118 132 10.0% -2.15 [-3.54, -0.76] Heterogeneity: Not applicable 118 132 10.0% -2.15 [-3.54, -0.76] Test for overall effect: $Z = 3.03 (P = 0.002)$ 118 132 10.0% -2.15 [-3.54, -0.76] 1.4.7 STEP UP in collateral ventilation positive Gompelmann 2016 14.6 5.92 35 19 4.7% 14.60 [3.00, 26.20] 1.4.7 STEP UP in collateral ventilation positive Gompelmann 2016 14.6 5.92 35 19 4.7% 14.60 [3.00, 26.20] Subtotal (95% CI) 35 19 4.7% 14.60 [3.00, 26.20] \checkmark Heterogeneity: Not applicable Est for overall effect: $Z = 2.47 (P = 0.01)$ \top \top \bullet \bullet Total (95% CI) 1236 856 100.0% 10.48 [7.07, 13.89] \bullet \bullet	Subtotal (95% CI)			208	107	10.1%	0.95 [-0.16, 2.06]		
BV Valve trial 2014 -2.15 0.7107 118 132 10.0% -2.15 [-3.54, -0.76] Ninane 2012 0 0 0 0 Not estimable Subtotal (95% CI) 118 132 10.0% -2.15 [-3.54, -0.76] Heterogeneity: Not applicable 118 132 10.0% -2.15 [-3.54, -0.76] Test for overall effect: Z = 3.03 (P = 0.002) 118 132 10.0% -2.15 [-3.54, -0.76] 14.7 STEP UP in collateral ventilation positive 35 19 4.7% 14.60 [3.00, 26.20] Gompelmann 2016 14.6 5.92 35 19 4.7% 14.60 [3.00, 26.20] Subtotal (95% CI) 35 19 4.7% 14.60 [3.00, 26.20] Image: Coll (Stopped Legendeity: Not applicable Test for overall effect: Z = 2.47 (P = 0.01) 1236 856 100.0% 10.48 [7.07, 13.89] Image: Coll (Stopped Legendeity	0 7 11	= 0.09)							
Winane 2012 0 0 0 0 Not estimable Subtotal (95% CI) 118 132 10.0% -2.15 [-3.54, -0.76] Heterogeneity: Not applicable 118 132 10.0% -2.15 [-3.54, -0.76] I.4.7 STEP UP in collateral ventilation positive Sompelmann 2016 14.6 5.92 35 19 4.7% 14.60 [3.00, 26.20] Subtotal (95% CI) 35 19 4.7% 14.60 [3.00, 26.20] Heterogeneity: Not applicable 35 19 4.7% 14.60 [3.00, 26.20] Fest for overall effect: Z = 2.47 (P = 0.01) 1236 856 100.0% 10.48 [7.07, 13.89]	1.4.6 Intrabronchial valves								
Ninane 2012 0 0 0 0 Not estimable Subtotal (95% CI) 118 132 10.0% -2.15 [-3.54, -0.76] Heterogeneity: Not applicable 118 132 10.0% -2.15 [-3.54, -0.76] I.4.7 STEP UP in collateral ventilation positive 5 5 19 4.7% 14.60 [3.00, 26.20] Subtotal (95% CI) 35 19 4.7% 14.60 [3.00, 26.20] Heterogeneity: Not applicable 35 19 4.7% 14.60 [3.00, 26.20] Fost for overall effect: Z = 2.47 (P = 0.01) 1236 856 100.0% 10.48 [7.07, 13.89]	BV Valve trial 2014	-2.15	0.7107	118	132	10.0%	-2.15 [-3.54, -0.76]	•	
Heterogeneity: Not applicable Test for overall effect: Z = 3.03 (P = 0.002) 1.4.7 STEP UP in collateral ventilation positive Gompelmann 2016 14.6 5.92 35 19 4.7% 14.60 [3.00, 26.20] Subtotal (95% CI) 35 19 4.7% 14.60 [3.00, 26.20] Heterogeneity: Not applicable 35 19 4.7% 14.60 [3.00, 26.20] Test for overall effect: Z = 2.47 (P = 0.01) 1236 856 100.0% 10.48 [7.07, 13.89]	Ninane 2012	0	0	0	0				
Test for overall effect: Z = 3.03 (P = 0.002) 1.4.7 STEP UP in collateral ventilation positive Gompelmann 2016 14.6 5.92 35 19 4.7% 14.60 [3.00, 26.20] Subtotal (95% CI) 35 19 4.7% 14.60 [3.00, 26.20] Image: Coll of the state	Subtotal (95% CI)			118	132	10.0%	-2.15 [-3.54, -0.76]	¢	
I.4.7 STEP UP in collateral ventilation positive Gompelmann 2016 14.6 5.92 35 19 4.7% 14.60 [3.00, 26.20] Subtotal (95% CI) 35 19 4.7% 14.60 [3.00, 26.20] Image: Coll of the state of		= 0.002)							
Gompelmann 2016 14.6 5.92 35 19 4.7% 14.60 [3.00, 26.20] Subtotal (95% CI) 35 19 4.7% 14.60 [3.00, 26.20] Image: Comparison of the comparison	,	,							
Subtotal (95% CI) 35 19 4.7% 14.60 [3.00, 26.20] Heterogeneity: Not applicable Total (95% CI) 1236 856 100.0% 10.48 [7.07, 13.89]		•	F 00	~-	10	4 -0/	44.00 10.00 00 00		
Test for overall effect: Z = 2.47 (P = 0.01) Total (95% CI) 1236 856 100.0% 10.48 [7.07, 13.89]	1	14.6	5.92						•
	• • •	= 0.01)							
	Fotal (95% CI)			1236	856	100.0%	10.48 [7.07, 13.89]	•	
Heterogeneity: Tau ² = 29.72; Chi ² = 160.59, df = 14 (P < 0.00001); l ² = 91% -100 -50 0 50	Heterogeneity: Tau ² = 29.72: Chi ²	= 160.59, df = 14 (P	< 0.0000	1); l² = 91%					50 10

Figure 3c. Efficacy outcomes of bronchoscopic lung volume reduction interventions in patients with severe emphysema: Percentage predicted FEV,

As reported by Kumar et al. [32] and Iftikhar et al. [33], segmental volume reduction by vapor ablation may appear as a promising approach in patients of upper lobe emphysema with positive collateral ventilation, but it needs to be further substantiated with large sample size randomized trials over a longer duration. Similar to Iftikhar et al. [33], discouraging

Chudu on Submany	BLVR		Standard Medica		Malala	Risk Ratio	Risk Ratio
Study or Subgroup 1.6.1 Bronchial Coils	Events	rotal	Events	iotal	weight	M-H, Random, 95% C	I M-H, Random, 95% CI
			10				
Deslee etal. 2016 (REVOLENS)	26	50	19	50	10.2%	1.37 [0.88, 2.13]	
Sciurba etal 2016 (RENEW)	54	158	30	157	10.8%	1.79 [1.21, 2.64]	
Shah etal. 2013 (RESET)	9	23	4	23	5.1%	2.25 [0.81, 6.28]	
Subtotal (95% CI)		231		230	26.0%	1.63 [1.23, 2.16]	\blacksquare
Total events	89		53				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.22$ Test for overall effect: Z = 3.43 (P = 0.0		= 0.54)	; l ² = 0%				
1.6.2 Bronchial Sealent							
Emphysematous Lung Sealant (ELS)	36	61	6	34	7.1%	3.34 [1.57, 7.12]	· · · · ·
Subtotal (95% CI)		61		34	7.1%	3.34 [1.57, 7.12]	•
Total events	36		6				
Heterogeneity: Not applicable							
Test for overall effect: $Z = 3.13$ (P = 0.0	002)						
· · · · · · · · · · · · · · · · · · ·							
1.6.3 Bronchial Vapor Ablation							
Herth etal. 2016 (STEP UP)	16	45	3	24	4.5%	2.84 [0.92, 8.80]	
Subtotal (95% CI)		45		24	4.5%	2.84 [0.92, 8.80]	
Total events	16		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.81 (P = 0.0	07)						
1.6.4 Bronchial Stent							
Shah etal. 2011 (EASE)	30	208	12	107	8.3%	1.29 [0.69, 2.41]	_ _
Subtotal (95% CI)	50	200	12	107	8.3%	1.29 [0.69, 2.41]	•
Total events	30	200	12		0.070		
	50		12				
Heterogeneity: Not applicable	40)						
Test for overall effect: Z = 0.79 (P = 0.4	43)						
1.6.5 Endobronchial valves							
	10	25	1	25	1.9%	10 00 11 20 72 201	
BeLieVeR HIFi 2015	10		1	25		10.00 [1.38, 72.39]	
IMPACT 2016	26	43	8	50	7.8%	3.78 [1.92, 7.46]	
LIBERATE 2018	94	128	34	62	12.1%	1.34 [1.04, 1.72]	-
STELVIO 2015	23	34	5	34	6.4%	4.60 [1.98, 10.68]	
TRANSFORM 2017	45	65	4	32	5.7%	5.54 [2.18, 14.05]	
VENT US 2010	13	220	4	101	4.7%	1.49 [0.50, 4.46]	
Subtotal (95% CI)		515		304	38.5%	3.13 [1.48, 6.60]	-
Total events	211		56				
Heterogeneity: Tau ² = 0.64; Chi ² = 28.7	70, df = 5 (P	o < 0.00	001); I² = 83%				
Test for overall effect: Z = 2.99 (P = 0.0	003)						
1.6.6 Intrabronchial valves							
IBV Valve trial 2014	20	142	5	135	5.6%	3.80 [1.47, 9.85]	
Ninane 2012	20 7	37	5	36	5.6% 4.4%	1.70 [0.54, 5.32]	
Subtotal (95% CI)	1	37 179	4	30 171	4.4% 10.0%	2.71 [1.24, 5.93]	
	07	113	0	171	10.070	2.1 1 [1.24, 0.30]	\bullet
Total events	27 1 - 14 - 1 (D	- 0.00	9				
Heterogeneity: Tau ² = 0.04; Chi ² = 1.14 Test for overall effect: Z = 2.49 (P = 0.0		= 0.28)	; 1² = 13%				
1.6.7 STEP UP in collateral ventilation	on positive						
Gompelmann 2016	9	35	5	19	5.6%	0.98 [0.38, 2.50]	
Subtotal (95% CI)	5	35	Ŭ	19	5.6%	0.98 [0.38, 2.50]	•
Total events	9		5			,	T
Heterogeneity: Not applicable	5		0				
Test for overall effect: $Z = 0.05$ (P = 0.5	96)						
	,	407			400.001	0 10 11 00 0 00	
Total (95% CI)		1274		889	100.0%	2.18 [1.63, 2.93]	
Total events	418		144				
Heterogeneity: Tau ² = 0.17; Chi ² = 36.6		P = 0.0	0008); I² = 62%				0.01 0.1 1 10 10
Test for overall effect: Z = 5.19 (P < 0.0	00001)						Favours [BLVR] Favours [Standard Care]
Test for subgroup differences: Chi ² = 9	.53, df = 6 (P = 0.1	15), I ² = 37.0%				

Figure 4a. Safety outcomes of bronchoscopic lung volume Reduction interventions in patients with severe emphysema: Total SAE

itudy or Subgroup	Endobroncl Events	nial T/t S Total	tandard Medica Events		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% Cl
.7.1 Bronchial Coils			-			. ,	
Deslee etal. 2016 (REVOLENS)	4	50	3	50	10.1%	1.33 [0.31, 5.65]	
ciurba etal 2016 (RENEW)	10	158	8	157	26.0%	1.24 [0.50, 3.06]	
hah etal. 2013 (RESET)	0	23	0	23		Not estimable	
ubtotal (95% CI)		231		230	36.1%	1.27 [0.59, 2.73]	-
otal events	14		11				
leterogeneity: Tau ² = 0.00; Chi ² = 0.01, fest for overall effect: Z = 0.61 (P = 0.54		94); l² = 0%)				
.7.2 Bronchial Sealent							
mphysematous Lung Sealant (ELS)	2	61	0	34	2.3%	2.82 [0.14, 57.15]	
Subtotal (95% CI)		61		34	2.3%	2.82 [0.14, 57.15]	
otal events	2		0				
leterogeneity: Not applicable							
est for overall effect: Z = 0.68 (P = 0.50	0)						
.7.3 Bronchial Vapor Ablation							
erth etal. 2016 (STEP UP)	2	45	0	24	2.4%	2.72 [0.14, 54.42]	
Subtotal (95% CI)	-	45	-	24	2.4%	2.72 [0.14, 54.42]	
otal events	2		0			-	
leterogeneity: Not applicable fest for overall effect: Z = 0.65 (P = 0.5	1)						
.7.4 Bronchial Stent							
shah etal. 2011 (EASE)	4	208	4	107	11.3%	0.51 [0.13, 2.02]	
Subtotal (95% CI)		208		107	11.3%	0.51 [0.13, 2.02]	
otal events	4		4				
leterogeneity: Not applicable							
Test for overall effect: $Z = 0.95$ (P = 0.34	4)						
.7.5 Endobronchial valves							
eLieVeR HIFi 2015	2	25	0	25	2.4%	5.00 [0.25, 99.16]	
MPACT 2016	0	43	1	50	2.1%	0.39 [0.02, 9.25]	· · · · · · · · · · · · · · · · · · ·
IBERATE 2018	5	128	1	62	4.7%	2.42 [0.29, 20.29]	
TELVIO 2015	1	34	0	34	2.1%	3.00 [0.13, 71.15]	· · · · · · · · · · · · · · · · · · ·
RANSFORM 2017	1	65	0	32	2.1%	1.50 [0.06, 35.83]	
'ENT EU 2012	6	111	4	60	14.1%	0.81 [0.24, 2.76]	
ENT US 2010	6	220	3	101	11.4%	0.92 [0.23, 3.60]	
ubtotal (95% CI)		626		364	38.8%	1.14 [0.55, 2.39]	-
otal events	21		9				
leterogeneity: Tau ² = 0.00; Chi ² = 2.68, est for overall effect: Z = 0.36 (P = 0.72		85); I² = 0%)				
.7.6 Intrabronchial valves							
3V Valve trial 2014	6	142	1	135	4.8%	5.70 [0.70, 46.76]	
inane 2012	1	37	0	36	2.1%	2.92 [0.12, 69.43]	
ubtotal (95% CI)		179		171	6.9%	4.65 [0.81, 26.82]	
iotal events	7		1				
leterogeneity: Tau ² = 0.00; Chi ² = 0.12, test for overall effect: Z = 1.72 (P = 0.09		73); I ² = 0%)				
.7.7 STEP UP in collateral ventilation	n positive						
Sompelmann 2016	1	35	0	19	2.1%	1.67 [0.07, 39.03]	
ubtotal (95% CI)		35		19	2.1%	1.67 [0.07, 39.03]	
otal events	1		0				
leterogeneity: Not applicable fest for overall effect: Z = 0.32 (P = 0.75	5)						
otal (95% CI)		1385		949	100.0%	1.25 [0.79, 1.99]	•
otal events	51		25				–
leterogeneity: Tau ² = 0.00; Chi ² = 7.30,).92); ² = ()					
est for overall effect: Z = 0.97 (P = 0.33		_,,. •					0.01 0.1 1 10 1 Favours [BLVR] Favours [Control]

Figure 4b. Safety outcomes of bronchoscopic lung volume reduction interventions in patients with severe emphysema: Death

results regarding the efficacy of stents in patients with severe homogeneous emphysema were observed in our review. Milenkovic et al. [35] reviewed bronchoscopic administration of lung sealants as an effective approach in patients with upper lobe emphysema with both heterogeneous and homogeneous distribution in patients with advanced emphysema. This could not be validated by this review because of the presence of limited evidence in form of prematurely terminated single trial with small sample size and high attrition (15).

Substantial heterogeneity (l^2 >50%) was observed for outcomes possibly due to varied inclusion and exclusion criteria of patients as per pattern of emphysema; the severity of disease (predicted FEV₁, RV and TLC); smoking status and compliance

	Endobronch			andard Medical Care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.9.1 Bronchial Coils							
Deslee etal. 2016 (REVOLENS)	1	50	3	50	9.1%	0.33 [0.04, 3.10]	
Sciurba etal 2016 (RENEW)	6	158	6	157	36.9%	0.99 [0.33, 3.01]	
Shah etal. 2013 (RESET)	0	23	0	23	001070	Not estimable	
Subtotal (95% CI)	Ŭ	231	0	230	46.0%	0.80 [0.30, 2.16]	-
Total events	7		9			0.00 [0.00, 2.10]	
		- 0 201	-				
Heterogeneity: Tau ² = 0.00; Chi ² =		= 0.39);	1- = 0%				
Test for overall effect: Z = 0.44 (P	= 0.66)						
1.9.2 Bronchial Sealent							
		•		•		Not estimable	
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicat	ole						
1.9.3 Bronchial Vapor Ablation							
Herth etal. 2016 (STEP UP)	0	45	0	24		Not estimable	
Subtotal (95% CI)	0	45 45	0	24 24		Not estimable Not estimable	
	^	40	^	24		Not estimable	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicat	ole						
1.9.4 Bronchial Stent							
Shah etal. 2011 (EASE)	4	208	0	107	5.4%	4.65 [0.25, 85.59]	
Subtotal (95% CI)	4	200 208	0	107	5.4%	4.65 [0.25, 85.59] 4.65 [0.25, 85.59]	
		200		107	J.4 /0	4.05 [0.25, 05.59]	
Total events	4		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.03 (P	= 0.30)						
1.9.5 Endobronchial valves							
BeLieVeR HIFi 2015	1	25	0	25	4.6%	3.00 [0.13, 70.30]	
IMPACT 2016	0	43	0	50		Not estimable	
LIBERATE 2018	3	128	2	62	14.6%	0.73 [0.12, 4.24]	
STELVIO 2015	0	34	0	34		Not estimable	
TRANSFORM 2017	0	65	0	32		Not estimable	
VENT EU 2012	4	111	1	52 60	9.7%	2.16 [0.25, 18.91]	
	4		2		9.7% 14.4%		
VENT US 2010 Subtotal (95% CI)	3	220 561	2	101 332	14.4% 43.3%	0.69 [0.12, 4.06] 1.06 [0.38, 2.95]	-
		301	-	332	40.0%	1.00 [0.30, 2.93]	
Total events	11		5				
Heterogeneity: Tau ² = 0.00; Chi ² =		= 0.74);	I ² = 0%				
Test for overall effect: Z = 0.11 (P	= 0.92)						
1.9.6 Intrabronchial valves							
IBV Valve trial 2014	4	142	0	135	5.4%	8.56 [0.47, 157.49]	
Ninane 2012	0	0	0	0	2.1.70	Not estimable	
Subtotal (95% CI)	v	142	v	135	5.4%	8.56 [0.47, 157.49]	
Total events	4		0				
Heterogeneity: Not applicable	4		U				
Test for overall effect: Z = 1.44 (P	= 0.15)						
	-	4407		000	400.00/	4 49 10 27 0 041	
Total (95% CI)	00	1187		828	100.0%	1.13 [0.57, 2.21]	\mathbf{T}
Total events	26	0.04	14				
Heterogeneity: Tau ² = 0.00; Chi ² =		= 0.61);	I ² = 0%				0.005 0.1 1 10 200
Test for overall effect: Z = 0.34 (P							

to pulmonary rehabilitation guidelines among participants. Also, varied definitions were adopted to estimate both efficacy and safety outcomes. For 6MWT, MCID of 54 m assessed by one trial [18] is more than double of the recommended MCID values for 6MWD (between 25 and 30 m) [36]. Standardized inclusion and exclusion criteria and outcome definition in future trials are thus warranted to assess clinical efficacy and safety of the BLVR interventions. The included trials did not account for the influence of co-morbidities on studied outcomes, and thus the observed effect in our review was unable

	Endobronchial T/t	Standard Medi			Risk Ratio	Risk Ratio
Study or Subgroup	Events Tota	Events	Total	Weight	M-H, Random, 95% C	I M-H, Random, 95% CI
1.8.1 Bronchial Coils						
Deslee etal. 2016 (REVOLENS)	22 50		50	8.9%	1.69 [0.96, 2.97]	
Sciurba etal 2016 (RENEW)	47 158	20	157	10.3%	2.34 [1.45, 3.75]	
Shah etal. 2013 (RESET)	7 23	3	23	3.2%	2.33 [0.69, 7.93]	
Subtotal (95% CI)	231		230	22.4%	2.06 [1.46, 2.92]	•
Fotal events	76	36				
Heterogeneity: Tau² = 0.00; Chi² = Fest for overall effect: Z = 4.09 (P		; I² = 0%				
1.8.2 Bronchial Sealent Subtotal (95% CI)	0		0		Not estimable	
Total events	0	0	· ·		Not ootimusio	
Heterogeneity: Not applicable Test for overall effect: Not applicat		U				
.8.3 Bronchial Vapor Ablation						
Herth etal. 2016 (STEP UP) Subtotal (95% CI)	19 45 45	3	24 24	3.8% 3.8%	3.38 [1.11, 10.27] 3.38 [1.11, 10.27]	
Fotal events	19	3	24	0.070	0.00 [111], 10.21]	
	19	3				
Heterogeneity: Not applicable Fest for overall effect: Z = 2.14 (P	= 0.03)					
1.8.4 Bronchial Stent						
Shah etal. 2011 (EASE) Subtotal (95% CI)	33 208 208	9	107 107	7.1% 7.1%	1.89 [0.94, 3.80] 1.89 [0.94, 3.80]	•
Total events	33	9				
leterogeneity: Not applicable Fest for overall effect: Z = 1.78 (P	= 0.08)					
.8.5 Endobronchial valves						
BeLieVeR HIFi 2015	18 25		25	13.1%	0.90 [0.66, 1.23]	
MPACT 2016	10 43	7	50	5.3%	1.66 [0.69, 3.99]	
IBERATE 2018	38 128	22	62	11.1%	0.84 [0.54, 1.28]	
STELVIO 2015	6 34	3	34	2.9%	2.00 [0.54, 7.35]	
RANSFORM 2017	7 65	3	32	3.0%	1.15 [0.32, 4.15]	
/ENT EU 2012	55 111	29	60	13.0%	1.03 [0.74, 1.41]	+
/ENT US 2010	22 220		101	6.3%	1.26 [0.58, 2.74]	
Subtotal (95% CI)	626	0	364	54.8%	0.99 [0.82, 1.19]	
Total events	156	92				
Heterogeneity: Tau ² = 0.00; Chi ² = Test for overall effect: Z = 0.09 (P	4.18, df = 6 (P = 0.65)					
.8.6 Intrabronchial valves						
BV Valve trial 2014	8 142	4	135	3.5%	1.90 [0.59, 6.17]	_ _
					1.34 [0.61, 2.94]	_ _
Vinane 2012 Subtotal (95% CI)	11 37 179		36 171	6.2% 9.6%	1.34 [0.61, 2.94] 1.49 [0.78, 2.87]	
			171	0.070	1.40 [0.70, 2.07]	
otal events Heterogeneity: Tau² = 0.00; Chi² = Fest for overall effect: Z = 1.20 (P		12; I ² = 0%				
.8.7 STEP UP in collateral venti	lation positive					
Gompelmann 2016	3 35	3	19	2.3%	0.54 [0.12, 2.43]	
Subtotal (95% CI) Fotal events	3 33 35 3		19	2.3%	0.54 [0.12, 2.43]	
	5	3				
Heterogeneity: Not applicable Fest for overall effect: Z = 0.80 (P	= 0.42)					
Fotal (95% CI)	1324		915	100.0%	1.37 [1.07, 1.75]	♦
Fotal events Heterogeneity: Tau ² = 0.09; Chi ² = Fest for overall effect: Z = 2.51 (P		155)2); I² = 49%				0.01 0.1 1 10 100 Favours [BLVR] Favours [Control]

Figure 4d. Safety outcomes of bronchoscopic lung volume reduction interventions in patients with severe emphysema: COPD exacerbations and LRTI

to report outcomes as per the health profile of participants. Also, the results of included trials are not stratified by age, sex, ethnicity, smoking status, and severity of disease that may reportedly influence studied outcomes [37-39]. Thus, this review cannot suggest optimum age, stage of disease, ethnic origin, and sex of a patient for whom the BLVR procedures will be more efficacious with minimum side effects.

Directions for future research

We suggest that the aforementioned limitations should guide future research especially those regarding EBV and EBCs. Future research should focus on optimizing four Ps for better interpretation of evidence, and to reach generalizability regarding available evidence. First P is recognizing patient characteristics by including a large sample size from multiple sites, both from developed and developing economies to stratify patient subgroups and thus getting maximum benefits from the BLVR procedures. Second P and third P are optimizing suitable BLVR Procedure and Provider experience and expertise in carrying out the procedure. This should be complemented with the fourth P in form of planned followup for early and successful diagnosis and management of potential complications either due to disease or due to the procedure. At present, evidence of the BLVR interventions is mainly available through studies carried out by an expert group in specialized centers. Research on patient population in less specialized centers and from developing economies is needed to justify the role of the BLVR interventions globally.

Bronchoscopic reduction of lung volume has emerged as a promising intervention for patients with advanced severe emphysema. Patient quality of life, exercise capacity, and lung function tests have been observed to improve with EBV at the cost of increased respiratory adverse events in patients with no collateral ventilation, and existing quality of evidence is high. EBC and TVA appear to be promising modalities, and large sample trials are needed in future to establish robust evidence. Optimizing patient selection for the specific bronchoscopic procedure with planned follow-up care to manage the higher risk of serious respiratory adverse events can prove beneficial for patients with advanced severe emphysema over standard medical care.

Key Message

Among patients with advanced severe emphysema, endobronchial valves and endobronchial coils have shown promising short-term improvement in important disease outcomes with increased risk of serious adverse events. Endobronchial coils are effective in both heterogeneous and homogeneous emphysema irrespective of collateral ventilation status, while endobronchial valves are effective only in patients without collateral ventilation. Among other modalities, bronchoscopic thermal vapor ablation appears promising, but it has not yet been adequately studied to derive any robust conclusion, while intra-bronchial valves, airway stents, and lung sealants are of no proven benefit. Although increased mortality was not observed with any of bronchoscopic procedures, long-term data are required to further substantiate the current findings.

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